## 2. RESPONSE/REMARKS

### 2.1 STATUS OF THE CLAIMS

***Claims 1-5 and 10-23 were pending at the time of the Action.***

***Claims 13 and 14 have been amended herein.***

***Claims 1-5 and 10-23 remain pending in the case.***

### 2.2 SUPPORT FOR THE CLAIMS

Support for the pending claims can be found throughout the original claims, specification and figures as filed. It will be understood that no new matter is included within any of the present claims.

### 2.3 THE OBJECTION TO CLAIMS 13 AND 14 IS OVERCOME.

***Claims 13 and 14 were objected to because of clarity. The Office has requested Applicants amend these claims to include "wherein said compounds have chemicals structures as follows:" language to improve their overall clarity.***

Without acquiescing in any way to the propriety of the request, and solely in the interest of advancing the pending claims to allowance, Applicants have amended claims 13 and 14 responsive to this request to insert the clarifying language as recommended by the Office.

Applicants believe this fully addresses Office's concern with respect to clarity, and respectfully requests that the objection be withdrawn.

## 2.4 THE REJECTION UNDER 35 U.S.C. § 103(A) IS OVERCOME.

***Claims 1, 2, and 6-23 were rejected under 35 U.S.C. § 103(a), allegedly as being obvious over Woodruff* et al. (Arth. & Rheum., *46:2476-85, 2002; hereinafter "Woodruff") in view of Farirlie* et al.(PCT Appl. Publ. No. WO 99/00406*; hereinafter "Fairlie") and Kivitz* et al. (J. Fam. Prac., *51:530-7, 2002; hereinafter "Kivitz").***

The Action considers that, while neither Woodruff nor Fairlie teach the use of AcF-[OPdChaWR] in the treatment of osteoarthritis, it would nevertheless have been obvious to one of ordinary skill in the art at the time of the invention to utilize such C5a receptor antagonists in a method for treating osteoarthritis. The Action states that the "skilled artisan would have been motivated to do so given the teaching of Kivitz *et al.* that pain and inflammation of rheumatoid arthritis and osteoarthritis patients can be treated with the same drugs, NSAIDs." The Action states that there "would have been a reasonable expectation of success given that Woodruff *et al.* teach that AcF-[OPdChaWR] can be used to treat inflammatory conditions."

Applicants respectfully traverse.

The Supreme Court has repeatedly concluded that a finding of obviousness is a question of law based on "underlying factual inquiries." The relevant factors to be considered were set forth over forty years ago in *Graham* v. *John Deere Co.* (383 U.S. 1, 148 USPQ 459, 1966) as follows: (a) determining the scope and content of the prior art; (b) ascertaining the differences between the claimed invention and the prior art; and (c) resolving the level of ordinary skill in the pertinent art.

These same *Graham* factors have also been applied in *each* of the Supreme Court's subsequent decisions regarding obviousness, including the widely-publicized *KSR International Co.* v. *Teleflex Inc.* [See *e.g., United States* v. *Adams, 383 U.S. 39, 51–52, 148 USPQ 479, 483*

*(1966); Sakraida* v. *Ag Pro, Inc.*, 425 U.S. 273, 189 USPQ 449, reh'g denied, 426 U.S. 955 (1976); *Dann* v. *Johnston*, 425 U.S. 219, 189 USPQ 257 (1976); *Anderson's-Black Rock, Inc.* v. *Pavement Salvage Co.*, 396 U.S. 57, 163 USPQ 673 (1969) and *KSR International Co.* v. *Teleflex Inc.*, 550 U.S. _, 82 USPQ2d 1385 (2007)][1].

In *KSR*, the Supreme Court concluded that the district court had correctly determined that the patent-in-suit was invalid as obvious, and that the Federal Circuit had erred in its decision (*Teleflex Inc.* v. *KSR Int'l Co.*, 119 Fed. Appx. 282, 288 [Fed. Cir. 2005]) overturning the lower court's finding by applying its longstanding "teaching-suggestion-motivation ("TSM") test" in an "overly rigid and formalistic way."

In *KSR*, the Supreme Court reaffirmed the familiar framework for determining obviousness as set forth in *Graham* based on its precedent that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." The Supreme Court further stated that:

> *"[w]hen a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, 35 U. S. C. § 103 bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill."*

When considering obviousness of a combination of known elements, the operative

[1]""In *United States* v. *Adams*, [t]he Court recognized that when a patent claims a structure already known in the prior art that is altered by the mere substitution of one element for another known in the field, the combination must do more than yield a predictable result. In *Anderson's-Black Rock, Inc.* v. *Pavement Salvage Co.*, [t]he two [pre-existing elements] in combination did no more than they would in separate, sequential operation. [I]n *Sakraida* v. *AG Pro, Inc.*, the Court derived the conclusion that when a patent simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious."" (*Id.* p. 57527; internal quotations omitted).

question is thus "whether the improvement is more than the predictable use of prior art elements according to their established functions."

Following the decision in *KSR,* the Office published revised examination guidelines on October 10, 2007 [Fed. Reg. **72(195)**:57526-57535] to assist Examiners in determining obviousness under 35 U.S.C. § 103 in view of the Supreme Court's latest decision. The revised guidelines note that when resolving the *Graham* inquiries,

> *"[i]t must be remembered that while the ultimate determination of obviousness is a legal conclusion, the underlying Graham inquiries are factual. When making an obviousness rejection, Office personnel must therefore ensure that the written record includes findings of fact concerning the state of the art and the teachings of the references applied. In certain circumstances, it may also be important to include explicit findings as to how a person of ordinary skill would have understood prior art teachings, or what a person of ordinary skill would have known or could have done. Factual findings made by Office personnel are the necessary underpinnings to establish obviousness."*
>
> *"In short, the focus when making a determination of obviousness should be on what a person of ordinary skill in the pertinent art would have known at the time of the invention, and on what such a person would have reasonably expected to have been able to do in view of that knowledge. This is so regardless of whether the source of that knowledge and ability was documentary prior art, general knowledge in the art, or common sense."*

In *KSR Int'l. Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1739 (2007), the Court stated that "a patent composed of several elements *is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.* Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, it can be important ***to identify a reason*** *that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.* This is so because inventions in most, if not all,

instances rely upon building blocks long since uncovered and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." *Id.* at 1741 (emphasis added).

As the PTO recognizes in M.P.E.P. § 2142:

> *"... [T]he examiner bears the initial burden of factually supporting any prima facie conclusion of obviousness. If the examiner does not produce a* prima facie *case, the applicant is under no obligation to submit evidence of non-obviousness..."*

If, however, the Examiner does produce a *prima facie* case, the burden of coming forward with evidence or arguments shifts to the applicant who may submit additional evidence of non-obviousness, showing that the claimed invention possesses improved properties not expected by the prior art. The initial evaluation of *prima facie* obviousness thus relieves both the Examiner and applicant from evaluating evidence beyond the prior art and the evidence in the specification as filed until the art has been shown to suggest the claimed invention:

> *"To reach a proper determination under 35 U.S.C. § 103, the Examiner must step backward in time and into the shoes worn by the hypothetical "person of ordinary skill in the art" when the invention was unknown and just before it was made. In view of all factual information, the Examiner must then make a determination whether the claimed invention as a whole would have been obvious at that time to that person. Knowledge of Applicant's disclosure must be put aside in reaching this determination, yet kept in mind in order to determine the "differences," conduct the search and evaluate the "subject matter as a whole" of the invention. The tendency to resort to hindsight based upon Applicant's disclosure is often difficult to avoid due to the very nature of the examination process. However, impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art"* (emphasis added).

> *"The ultimate determination of patentability is based on the entire record, by a preponderance of evidence, with due consideration to the persuasiveness of any arguments and any secondary evidence.* In re Oetiker, *977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). The legal standard of "a preponderance of evidence" requires the evidence to be more convincing than the evidence which is*

> *offered in opposition to it. With regard to rejections under 35 U. S. C. § 103, the Examiner must provide evidence which as a whole shows that the legal determination sought to be proved (i.e., the reference teachings establish a prima facie case of obviousness) is more probable than not*" (emphasis added).

In the present application, Applicants respectfully assert that the legal standard required for sustaining a rejection of the pending claims for obviousness as a matter of law has not been met. Moreover, Applicants believe that the cited references also fail to obviate the claimed invention based upon matters of fact.

### 2.4.1 THE OFFICE HAS NOT SHOWN HOW THE ELEMENTS BEING COMBINED PRODUCE A PREDICTABLE RESULT.

M.P.E.P. § 2143.01(III) states that "the mere fact that references *can be combined* does not render the resultant combination obvious *unless the results would have been predictable* to one of ordinary skill in the art." In the present case, the Office has not provided any evidence or clear reasoning why combining the teachings of Woodruff and Fairlie with those of Kivitz in *any* way would present a predictable result, or render the claimed invention legally obvious.

The Office has not shown how it would have been obvious to one of ordinary skill in the art that the combination of the three cited references would have provided a *predictable* result in a method for treating a disease that was not even mentioned in the Woodruff and Fairlie documents. The Office considers only that the references *could* be combined in some fashion so as to make the invention obvious to one of ordinary skill in the art; not how combining these teachings *would* have caused one of ordinary skill in the art to achieve the claimed methods *predictably*, and without any further improvement, assessment, development or experimentation.

For this reason alone, the Examiner's burden of factually supporting a *prima facie* case of obviousness has not been met, and as such the rejection under 35 U.S.C. § 103(a) should be withdrawn.

Moreover, the Office has concluded that one of ordinary skill would have done so ***not only with the expectation of success, but also with an ability to predict the outcome of the invention***. The Office concludes that the claimed methods for treating osteoarthritis as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made in view of the disclosures of Woodruff, Fairlie, and Kivitz.

In response to these rejections, Applicants respectfully disagree, and traverse each of them. The Applicants believe that the Office is using the impermissible benefit of hindsight reconstruction, selectively choosing excerpts from the cited references to advance rejection of various pending claims based upon legal obviousness using the cited references.

To address the issue, Applicants have submitted a third-party Declaration by a well-known expert in Applicants' field, that respectfully asserts the combination of the three cited references would have been insufficient to motivate one of ordinary skill in the art to conclude that the invention was *prima facie* obvious at the time it was made based upon the combination of the Woodruff, Fairlie, and Kivitz references relied upon by the Office.

### 2.4.2 A THIRD-PARTY DECLARATION UNDER 37 C.F.R. § 1.132 IS PROVIDED.

To rebut the prior art rejections advanced over the references cited *supra*, Applicants have provided an independent, third-party Declaration pursuant to 37 C.F.R. § 1.132 (attached hereto as **Appendix A**) prepared by Richard O. Day, Ph.D.[1]

For nearly two decades, Dr. Day has been a Professor of Clinical Pharmacology at the University of New South Wales, located in New South Wales, Australia; his research is the subject of more than 300 academic publications. Dr. Day has distinguished himself in the disciplines of medicine and clinical pharmacology, and is well-known in the Applicants' field of study. Evidence of Professor Day's extensive credentials in the field is provided in his *curriculum vitae,* which is attached to **Appendix A** as "**Exhibit RD1.**"

**Exhibit RD1** clearly demonstrates Dr. Day is well-suited for the purpose of addressing on both the medical and technical bases, the specific concerns that have been raised by the Office during its examination of the merits of the instant application.[2]

The Applicants further believe that Dr. Day's career in this discipline also qualifies him to address particular issues such as: (a) what the skilled artisan would have known in this particular research area at the time the present application and its priority applications were filed; (b) what a skilled artisan would be able to ascertain through a critical review of the instant Specification, claims and drawings; (c) whether the combination of references cited by the Examiner does, in fact, suggest elements of the claimed invention; and (d) whether the issue raised by the Office regarding obviousness of the claimed invention by the cited documents is valid in his expert opinion.

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[1]Declaration at ¶ 1.
[2]*Ibid.* at ¶¶ 2-3.

In submitting the declaration by Professor Day, the Applicants have sought to address Examiner Bradley's specific concern of obviousness over the combination of cited references by providing an independent, third-party declaration from an independent research scientist who *clearly* meets the standard of "one of ordinary skill in the art" in the field relevant to the instant invention.

Turning to the highlights of Dr. Day's scientific analysis of the specification, the claims, and the cited prior art, he states in his Declaration that he has reviewed the pending application and the instant non-final Action, and has also considered the various rejection of pending claims allegedly as being obvious over a combination of the three cited references.[1]

The Declarant notes that while he agrees that "(Fairlie) refers to the compound AcF-[OPdChaWR] and shows that the compound has a C5aR affinity of 0.3 μM;" (r)elevantly, however, this reference has no information regarding the treatment of osteoarthritis."[2]

Dr. Day continues his analysis of the present rejection by stating that he disagrees with the Examiner's conclusions that claimed invention is obvious in view of the cited art. He states that "Kivitz et al. states that pain and inflammation of rheumatoid arthritis and osteoarthritis patients can be treated with the same drugs, namely NSAIDs. From this disclosure the Examiner appears to be suggesting that it would be obvious to use a particular agent in the treatment of osteoarthritis if that agent had been used in the treatment of rheumatoid arthritis.[3] Prof. Day further notes "(w)ith respect, I disagree with the Examiner's assumptions. Osteoarthritis is a very different disease to rheumatoid arthritis. In particular I do not believ (*sic*) the combination

[1] *Ibid.* at ¶¶ 4-6.
[2] *Ibid.* at ¶ 7.
[3] *Ibid.* at ¶ 8.

of these three references provides any basis for a belief that AcF-[OPdChaWR[ or another C5a receptor antagonist could be used to treat osteoarthritis."[1]

The Declarant then goes on to describe in detail the difference between osteoarthritis and rheumatoid arthritis, and discusses differences in the underlying pathological processes associated with progress of the diseases. Prof. Day notes that unlike osteoarthritis, rheumatoid arthritis is a chronic autoimmune disease, "which manifests itself as inflammation of the synovial membrane lining the joints." He notes that the inflammation "causes joint swelling, pain and stiffness, the latter notably and in contrast to osteoarthritis, in the morning."[2]

The Declarant next discusses a paper by Schwartzman *et al.* (hereinafter "Schwartzman")[3] attached to his declaration as "**Exhibit RD2**." In this paper, he notes that three TNF agents are currently available in the United States that are available for treating rheumatoid arthritis.[4] Prof. Day states that although "(i)nfliximab, etanercept and adalimumab are each indicated for rheumatoid arthritis, none are indicated for osteoarthritis." (Emphasis added).

Similarly, he notes "(g)iven the difference between these two disease states, it is not possibly to simply extrapolate from one disease to the other."

Thus, for the reasons set forth in the accompanying statement, and in those already of record, the Applicants respectfully request that the obviousness rejection be withdrawn.

---

[1] *Ibid.* at ¶ 9.
[2] *Ibid.* at ¶ 10.
[3] *Arthritis Res. Ther.*, **6(Suppl 2):**S3-S11, 2004.
[4] Declaration at ¶¶ 11-12.

### 2.4.3 THE THIRD-PARTY DECLARATION EFFECTIVELY REBUTS *PRIMA FACIE* OBVIOUSNESS.

The value of factual knowledge of those skilled in the art, as set forth in an affidavit or declaration, is well established under the law.[1] In the *Katzschmann* decision, made in connection with overturning a rejection under 35 U. S. C. § 103(a), the court stated:

> "We do not think it was the intent of § 103 that either the examiner, the Board or this Court should substitute their own speculations for the factual knowledge of those skilled in the art."[2]

Therefore, even if the Office was held to have established a reasonable *prima facie* obviousness rejection, submission of a Declaration by a recognized third-party expert is sufficient to overcome such a rejection.[1]

To that end, Applicants respectfully assert that the accompanying Declaration of Dr. Richard O. Day effectively rebuts the outstanding obviousness rejection under 35 U. S. C. § 103(a). As noted above, Dr. Day's Statement explains that, given the disclosures of the three cited documents, it would have been highly unlikely that a person of ordinary skill in the art intent on progressing research in a useful way, would have been motivated by the teachings of Woodruff, Fairlie and Kivitz to develop a method for treating osteoarthritis using C5a receptor antagonists with a reasonable expectation of success in achieving the claimed methods for treating such a disease.

Dr. Day explains that, in comparison to the surprising and unexpected advances achieved in the present application, combination of the cited references would ***not*** have motivated the skilled artisan to arrive at Applicants' invention as presently claimed.

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[1] *In re Katzschmann*, 146 USPQ 66 (C.C.P.A. 1965); *In re Soni*, 34 USPQ2d 1684, 1688 (Fed. Cir. 1995).
[2] *Ibid.* 146 USPQ at 68.

As stated in his Declaration, "(g)iven the very different nature of the two diseases, rheumatoid arthritis and osteoarthritis, there is no reason to believe that the complement system is also involved in osteoarthritis in a fundamental way. Without knowledge that the complement system is involved in osteoarthritis, in my opinion there is nothing to lead a person to use a C5a receptor antagonist in the treatment of osteoarthritis."[2]

Therefore, in view of the Declarant's opinion that the combination of references would ***not*** have rendered the claimed methods obvious, and that a person of ordinary skill in the art would ***not*** have been motivated to combine the various elements of the cited references to produce the claimed subject matter, Applicants now respectfully request that the obviousness rejection be withdrawn.

## 2.5 CONCLUSION

It is respectfully submitted that the pending claims are fully enabled by the Specification, that all pending claims are definite, and free of the cited prior art. Applicants believe this to be a complete and timely reply to the pending Action, and assert the claims are acceptable under all sections of the Statutes and in conditions for allowance. Applicants respectfully request the withdrawal of all rejections of record.

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[1] *In re Katzschmann and In re Soni, supra.*
[2] Declaration at ¶ 13.

Should the Examiner have any questions, a telephone call to the undersigned Applicants' representative would be appreciated.

Respectfully submitted,

Mark D. Moore, Ph.D.
Registration No. 42,903

**Date: September 11, 2008**
HAYNES AND BOONE, LLP
Customer No. 27683
Telephone: 713-547-2040
Facsimile: 214-200-0853
H-745217v1

**Certificate of Service**

I hereby certify that this correspondence is being filed with the U.S. Patent and Trademark Office *via* EFS-Web on September 11, 2008.

Margaret A. Pruitt

# APPENDIX A

(PATENT)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of:
Ian Alexander SHIELS et. al.

Application No.: 10/531,560 Confirmation No.: 3534

Filed: 27 January 2006 Art Unit: 1654

For: TREATMENT OF OSTEOARTHRITIS Examiner: Christina BRADLEY

**DECLARATION OF RICHARD DAY PURSUANT TO 37 C.F.R. 1.132**

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, **Richard Day**, declare as follows:

I am currently Professor of Clinical Pharmacology at the University of New South Wales located in New South Wales, Australia, a position I have held since 1990. I am also Director of Clinical Pharmacology & Toxicology at St Vincent's Hospital, located in Sydney. I have a clinical practice in Clinical Pharmacology, Rheumatology and Pathology at St Vincent's Hospital, located in Sydney. I was Chair of the Pharmaceutical Health and Rational Use of Medicines Committee (PHARM) between 1999 and 2008. PHARM is an expert committee providing advice to the Australian Federal Government on how to achieve quality use of medicines. I also sat on the "Committee of Chairs" together with the Chairs of the

NPS, APAC and PBAC which also advised the Australian Federal Government and co-coordinated activities in the sector of the quality use of medicines (1999-2007).

I have held a number of positions as a Director, Chairman and Board Member of various government and private organizations as detailed in my *curriculum vita* attached herewith.

My scientific expertise includes the fields of medicine and medications. My particular fields of expertise include the mechanisms and pharmacological treatments of rheumatic diseases which range across studies in inflammation, musculoskeletal pain, non-steroidal anti-inflammatory drugs (NSAIDs), anti-rheumatic drugs and hypouricaemic therapies. My research is the subject of over 300 publications.

I have read US patent application No 10/531,560 and understand it to be directed to a method of treating osteoarthritis using C5a receptor antagonists.

I have also read and understood the Examiner's objection in the Official Action issued by the USPTO on 13 March 2008 in respect of US patent application No 10/531,560.

I understand that the Examiner considers that it would be obvious to use the peptide AcF-[OPdChaWR] to treat osteoarthritis on the basis of the work of Woodruff, T., M., *et. al. Arthritis & Rheumatism* (2002) 46: 2476 – 85 the use of AcF-[OPdChaWR] to treat rheumatoid arthritis. I understand from the teachings of Woodruff, T. M., *et. al.*, that AcF-[OPdChaWR] is a C5a receptor antagonist.

In raising this allegation of obviousness I understand the Examiner also relies on Fairlie *et al* WO 99/00406. I agree with the Examiner that this reference refers to the compound AcF-[OPdChaWR] and shows that the compound has a C5aR affinity of 0.3 μM. Relevantly, however, this reference has no information regarding the treatment of osteoarthritis.

I understand that the Examiner also considers that Kivitz, A., *et. al. Journal of Family Practice* (2002) June Vol. 51 No. 6: 530 – 537 to be relevant to determining whether it was obvious to use a C5a receptor antagonist in the treatment of osteoarthritis. Kivitz, *et al* states that pain and inflammation of rheumatoid arthritis and osteoarthritis patients can be treated with the same drugs, namely NSAIDs. From this disclosure the Examiner appears to be suggesting it would be obvious to use a particular agent in the treatment of osteoarthritis if that agent had been used in the treatment of rheumatoid arthritis.

With respect, I disagree with the Examiner's assumptions. Osteoarthritis is a very different disease to rheumatoid arthritis. In particular I do not believ the combination of these three references provides any basis for a belief that AcF-[OPdChaWR] or another C5a receptor antagonist could be used to treat osteoarthritis

Osteoarthritis is a chronic degenerative disease affecting joints. For this reason osteoarthritis is also known as degenerative joint disease. In osteoarthritis the cartilage between the joints degenerates as the primary outcome of the pathophysiologic processes of osteoarthritis. Bone spurs, also known as osteophytes, are produced and fluid commonly accumulates in the joint spaces at the same time as the cartilage is destroyed. These pathological processes of formation of bone spurs, fluid accumulation in joints and cartilage degeneration and loss are associated with pain and often evidence of inflammation in the patient as the disease progresses. Inflammation is not the primary pathophysiologic process in osteoarthritis. The cartilage in joints may degenerate due to stress on the joint or injury to the joint but there are other factors that are important such as genetic constitution of the individual.

Rheumatoid arthritis, in contrast to osteoarthritis, is a chronic autoimmune disease which manifests itself as inflammation of the synovial membrane lining the joints and this is known as synovitis. The inflammation causes joint swelling, pain and

stiffness, the latter notably and in contrast to osteoarthritis, in the morning. The underlying cause of rheumatoid arthritis is not clearly understood but there are genetic factors involved and these are different from those relevant to osteoarthritis. A patient with rheumatoid arthritis may be prescribed a non-steroidal anti-inflammatory drug (NSAID) to treat the inflammation and associated pain. However NSAIDs do not halt the progression of rheumatoid arthritis. To tackle the underlying process of the disease causing synovitis and then damage to the joint, anti-TNF agents have been employed to reduce joint inflammation in rheumatoid arthritic patients by blocking TNF. TNF is a protein that is an important driver of inflammation as a result of the body's normal immune response. But in the case of rheumatoid arthritis the TNF production continues and drives the synovitis and eventually damage to the joints.

Schwartzman, S., *et. al. Arthritis Res. Ther.* (2004) Vol. 6 Suppl. 2: S3 – S-11 (online article) now shown to me and attached herewith, discusses the efficacy of three TNF agents currently available in the United States of America to treat rheumatoid arthritis. The three TNF agents are infliximab, etanercept and adalimumab. The indications for each of these agents may be accessed from the Drugs.com website but for convenience an online printout for each agent is now shown to me and attached herewith. Infliximab, etanercept and adalimumab are each indicated for rheumatoid arthritis however none are indicated for osteoarthritis.

The etiologies of rheumatoid arthritis and osteoarthritis are very different. Osteoarthritis is a degenerative disease whereas rheumatoid arthritis is an autoimmune inflammatory disease. Given the difference between these two disease states, it is not possible to simply extrapolate from one disease to the other.

In my view, the Kivitz *et al* paper says nothing more than NSAIDs may be used to treat inflammation in both rheumatoid arthritis and osteoarthritis. It is hardly surprising that an anti-inflammatory agent can be used to treat inflammation in two

different disease states. There is much less inflammation in osteoarthritis and inflammation is a secondary process in osteoarthritis in comparison to rheumatoid arthritis. Also, NSAIDs are used successfully for their analgesic properties in osteoarthritis even when there is little evidence of inflammation present.

The situation in the present case is very different. The teaching of Woodruff *et al* is that a C5a receptor antagonist is useful in the treatment of rheumatoid arthritis. As explained on page 2476 of this article, rheumatoid arthritis is an immunological disorder involving local activation of inflammatory cells. The complement system, and in a particular the factor C5a, has long been identified as a likely contributor to the pathogenesis of rheumatoid arthritis. Accordingly, it follows that a C5a receptor antagonist would be expected to be useful in the treatment of rheumatoid arthritis.

Given the very different nature of the two diseases, rheumatoid arthritis and osteoarthritis, there is no reason to believe that the complement system is also involved in osteoarthritis in a fundamental way. Without knowledge that the complement system is involved in osteoarthritis, in my opinion there is nothing to lead a person to use a C5a receptor antagonist in the treatment of osteoarthritis. The fact that anti-inflammatories such as NSAIDs may be used to treat symptoms in both osteoarthritis and rheumatoid arthritis is largely irrelevant. In neither case will NSAIDs slow the progress of disease. The analgesic effects of NSAIDs in osteoarthritis are independent of whether there is any inflammation present at all. In order for a person to use a C5a inhibitor in the treatment of osteoarthritis they would need some suggestion or information that complement was involved in osteoarthritis. I am not aware that such information was available prior to this application.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001

of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

Dated: 11th of September 2008
[Day, Month, Year]

By: Ric Day
[Signed by Richard Day]

# EXHIBIT RD1

**RICHARD DAY** is Professor of Clinical Pharmacology at UNSW and Director of Clinical Pharmacology & Toxicology at St Vincent's Hospital Sydney. He has a clinical practice in Clinical Pharmacology, Rheumatology and Pathology at St Vincent's Hospital. He was chairman of the Research Ethics Committee at St Vincent's Hospital (1990-1996) and a member of the UNSW Ethics Committee.

He sat on the Training Awards (1994-1999) and on the Research Ethics Subcommittee's (1995-1997) of the NH&MRC. He was chairman of the review of the Clinical Trials Notification Scheme for the Federal Department of Health's Therapeutic Goods Association (1993) and has chaired a review of the Pharmaceutical Services Branch of the NSW Department of Health (1996/7). He was a Director of the MBF (1998-2003).

Professor Day chaired the Pharmaceutical Health and Rational Use of Medicines Committee (PHARM), an expert committee advising the Federal Government on how to achieve 'quality use of medicines' (QUM; 1999-2008). He sat on the 'Committee of Chairs' along with the chairs of NPS, APAC and PBAC, which also advises the Federal Government and co-ordinates activities in this sector of QUM during this time. He was a Board member (1999-2000; 2001-2004; 2004-2007) of the DIA (Drug Information Association), an international association of over 24,000 members and past chair of the South West Asian Pacific Committee of the DIA.

Professor Day has a particular interest in promoting the quality of use of medicines by prescribers and in the community which has found expression in membership of PHARM, chairmanship of the St Vincent's Hospital Drug Committee (1994-2003), clinical director of the NSW Medicines Information Centre (MIC), director of the St Vincent's clinical trials centre, membership of Australian Drug Evaluation Committee (ADEC-1991-1996), independent member of the Medicines Australia (MA) Code of Conduct Subcommittee and chairmanship of NSW Therapeutic Assessment Group (NSWTAG; 1992-1999). More recently he has co-chaired the Medication Safety Taskforce of the Australian Safety and Quality Council for the Federal government (2002-2004) and was appointed chair of the NSW Medication Safety Committee in 2008. His professional life has focussed on teaching QUM in innovative ways to medical students at UNSW and its teaching hospitals. He has 'taught' QUM in multiple other venues across all stakeholder groups for many years – most recently with Diabetes Educators at their annual meeting.

He has research interests into the mechanisms and pharmacological treatments of the rheumatic diseases which have ranged across studies in inflammation, musculoskeletal pain, NSAIDs, antirheumatic drugs, and hypouricaemic therapies and has published over 300 papers.

## Publications


Brooks PM, **Day RO.** Non Steroidal Anti-inflammatory drugs-Differences and similarities? *N Engl J Med* 1991; 324: 1716-1725

Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, **Day R**, Ferraz MB, Hawkey CJ, Hochberg MC, Kvien TK, Schnitzer TJ, Weaver A. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *New Engl J Med* 2000; 343(21):1520-1528

**Day RO**, Brooks P, Conaghan PG, Petersen M. A double-blind, randomised, parallel group study of the effectiveness and tolerance of intra-articular hyaluronan in osteoarthritis of the knee. *Journal of Rheumatology* 2004; 31(4):775-82,2004.

Lee EJD, Williams KM, **Day RO**, Graham GG, Champion GD. Stereoselective disposition of ibuprofen enantiomers in man. *Br J Clin Pharmacol* 1985; 19: 669-674. (Citations Dec 1993; 117)

Johnson AG, Nguyen T, **Day RO.** Do non-steroidal anti-inflammatory drugs affect blood pressure. A meta-analysis? *Annals Int Med* 1994; 121: 289-300


## Grants

| | |
|---|---|
| 352576 NH&MRC 05-07 | Maher C, Latimer J, McLachlan A, Day R, Cooper C; Project: A clinical trial of manipulative therapy and/or NSAIDs for significant acute low back pain.2005: $183,438.00; 2006: $208,438.00; 2007: $79,938.00 |
| 401020 NH&MRC 06-08 | M Lassere, N Bellamy, R Day, R Iedema, K Johnson, P Tugwell; Project Grant; Measuring adverse events: development of a patient-centred adverse event reporting tool (PAET); 2006 $181,500, 2007 $163,750, 2008 ($93,250) |
| 402511 NH&MRC 06-10 | M Fransen, R Day, J Edmonds, C Bridges-Webb, R Norton, M Woodward; Project Grant; Long term effect of Glucosamine Sulphate (LEGS) study; 2006 $340,963, 2007 $312,038, 2008 $277,083, 2009 ($192,038), 2010 ($52,833): |
| 400929 NH&MRC 06-08 | Westbrook J, Runciman W, Day R, Dunsmuir W, Braithwaite J, Williamson M; Project: The safety and effectiveness of hospital e-prescribing systems: a controlled time series study. 2006 ($194,100), 2007 ($207,400), 2008 ($190,200) |
| 300435 NH&MRC | EW Coiera, JI Westbrook, MR Kidd, R. Day; Project: Changing decision-making behaviour in primary care by providing access to online evidence; 2004: $179,500.00; 2005: $164,500.00; 2006: |

**References**

**Full papers only from 1991**


P64. Winn J, Guille J, Day RO, Gebicki J. Hydrogen peroxide modulation of the respiratory burst of human neutrophils. *Biochem Pharmacol* 1991; 41: 31-36

P65. Williams KM, Day RO, Knihinicki RD. Pharmacokinetics of the enantiomers of ibuprofen in the rabbit. *Agents Actions* 1991; 34: 381-386

P66. Zhao B, Geisslinger G, Hall I, Day RO, Williams KM. The effects of the enantiomers of ibuprofen and flurbiprofen on the B-oxidation of palmitate in the rat. *Chirality* 1992; 4: 137-141

P67. Australian Multicentre Trial Group (Day RO a member). Sulphasalazine in early rheumatoid arthritis. *J Rheumatol* 1992; 19: 1672-1677

P68. Hicks M, Wong L, Day RO. Antioxidant activity of propylthiouracil. *Biochem Pharmacol* 1992; 43: 439-444

P69. Lau A, Graham GG, Day RO, Perry MA. Effect of aspirin on ulcer site blood flow in cat stomachs. *Am J Physiol* 1992; 263: G155-G160

P70. Sandhu GS, Day RO. Factors affecting prescribing in general practice-a role play. *Med J Aust* 1992; 157: 621-622

P71. Tett SE, Cutler DJ, Day RO. Bioavailability of hydroxychloroquine tablets assessed using deconvolution techniques. *J Pharm Sci* 1992; 81: 155-159

P72. Tett S, McLachlan A, Day RO, Cutler D. Insights from pharmacokinetic and pharmacodynamic studies of hydroxychloroquine. In: Variability in response to antirheumatic drugs Eds PM Brooks, RO Day, KM Williams, GG Graham *Agents & Actions* 1993; Suppl 44: pp 145-150

P73. Walker JW, Arroyo JF, Nguyen TV, Day RO Analgesic efficacy of non-steroidal anti-inflammatory drugs in experimental pain in humans *Brit J Clin Pharmacol* 1993; 36: 417-426

P74. Day RO, Wacher A, Cairns D, Connors G, McGrath M. Nailfold capillary circulation in osteoarthritis. *Br J Rheumatol* 1993; 32: 1062-1065

P75. Hicks MH, Wong LS, Day RO. Suitability of reverse-phase columns from different sources for separation of uric acid from its oxidation products. *Analyt Biochem* 1993; 210: 428-430

P76. Hicks M, Wong LS, Day RO. Identification of products from oxidation of uric acid induced by hydroxyl radicals. *Free Radicals Res Communics* 1993; 18: 337-351

P77. Johnson AG, Nguyen TV, Day RO. Evaluation of the accuracy and reproducibility of ambulatory blood pressure monitoring in the very elderly using the Takeda TM-2420. *J Human Hypertension* 1994; 8: 433-439

P78. Tett SE, Day RO, Cutler DJ. Concentration-effect relationship of hydroxychloroquine in rheumatoid arthritis - a cross sectional study. *J Rheumatol* 1993; 20: 1874-1879

P79. Walker JS, Knihinicki R, Seideman P, Day RO. Pharmacokinetics of ibuprofen enantiomers in plasma and suction blister fluid in healthy volunteers. *J Pharm Sci* 1993; 82: 1-4

P80. Handel ML, Sivertsen S, Watts CKW, Day RO, Sutherland RL. Comparative effects of gold on the interactions of transcription factors with DNA
In: Variability in response to antirheumatic drugs Eds RO Day, PM Brooks, KM Williams, GG Graham. *Agents & Actions*, Suppl, 1993; 44: 219-223

P81. McLachlan AJ, Tett SE, Cutler DJ, Day RO. Disposition of the enantiomers of hydroxychloroquine in patients with rheumatoid arthritis following multiple doses of the racemate. *Brit J Clin Pharmacol* 1993; 36: 78-81

P82. McLachlan AJ, Tett SE, Cutler DJ, Day RO. Absorption and *in vivo* dissolution of hydroxychloroquine in fed subjects assessed using deconvolution techniques. *Brit J Clin Pharmacol* 1993; 36: 405-412

P83. McLachlan AJ, Tett SE, Day RO, Cutler DJ. Interpretation of chloroquine pharmacokinetic data (letter). *European J Clin Pharmacol* 1993; 44: 407-408

P84. Johnson AG, Nguyen T, Day RO. Do non-steroidal anti-inflammatory drugs affect blood pressure. A meta-analysis? *Annals Int Med* 1994; 121: 289-300

P85. Day RO, Geisslinger G, Paull P, Williams K. Neither cimetidine nor probenecid affect the pharmacokinetics of tenoxicam in normal volunteers. *Brit J Clin Pharmacol* 1994; 37: 79-81

P86. McLachlan AJ, Tett SE, Cutler DJ, Day RO. Disposition and absorption of hydroxychloroquine enantiomers following a single dose of the racemate. *Chirality* 1994; 6: 360-364

P87. Tett SE, McLachlan AJ, Cutler DJ, Day RO Pharmacokinetics and pharmacodynamics of hydroxychloroquine enantiomers in patients with rheumatoid arthritis receiving multiple doses of racemate. *Chirality* 1994; 6: 355-359

P88. Walker JW, Nguyen TV, Day RO. Clinical response to non-steroidal anti-inflammatory drugs in urate-crystal induced inflammation: a simultaneous study of intersubject and intrasubject variability. *Brit J Clin Pharmacol*, 1994; 38: 341-347

P89. McLachlan AJ, Tett S, Cutler D, Day RO. Bioavailability of hydroxychloroquine tablets in patients with rheumatoid arthritis. *Br J Rheumatol* 1994; 33: 235-239

P90. Seideman P, Lohrer F, Graham GG, Duncan MW, Williams KM, Day RO. The stereoselective disposition of the enantiomers of ibuprofen in blood, blister and synovial fluid. *Brit J Clin Pharmacol* 1994; 38: 221-227

P91. Johnson AG, Day RO. Response to a Recent Commentary by Drs O'Brien and Atkins 1995; 9: 205 (Letter) Re - Johnson AG, Nguyen TV, Day RO. Evaluation of the Accuracy and Reproducibility of the Takeda TM-2420 in the Elderly. *J Hum Hypertens* 1994; 8: 433-439

P92. McLachlan AJ, Tett S, Cutler DJ, Day RO. In vivo and in vitro disposition of hydroxychloroquine enantiomers; single dose kinetics following racemate administration and aspects of distribution. *Chirality* 1994; 6: 360-364

P93. Walker JS, Nguyen T, Day RO. Variability in response to ibuprofen in experimentally-induced inflammation on human volunteers. *Br J Clin Pharmacol* 1994; 38: 1-5

P94. Handel ML, Watts CKW, DeFazio A, Day RO, Sutherland RL. Inhibition of AP-1 binding and transcription by gold and selenium involve conserved cysteine residues in Jun and Fos. *Proc Nat Acad Sci* 1995; 92(10): 4497-4501

P95. Day RO, Geisslinger G, Paull P, Williams KM. The effect of tenoxicam on tolbutamide pharmacokinetics and glucose concentrations in healthy volunteers. *Int J Clin Pharmacol Therap* 1995; 33(5): 308-310

P96. Johnson AG, Nguyen T, Day RO. Non-steroidal anti-inflammatory drugs and high blood pressure (letter) *Annals Int Med* 1995; 122: 397

P97. Day RO, Francis H, Vial J, Geisslinger G, Williams KM. Naproxen concentrations in plasma and synovial fluid and effects on prostanoid concentrations. *J Rheumatol.* 1995; 22: 2295-2303

P98. Johnson AG, Nguyen TV, Day RO. Evaluation of the Takeda TM-2420 in the Elderly. *J Hum Hypertens* 1996; 10: 61

P99. Walker JS, Day RO. Experimental Pain techniques. *Brit J Clin Pharmacol* 1996; 41:349-350

P100. McManus P, Primrose JG, Henry DA, Birkett DJ, Lindner J, Day RO. Pattern of non-steroidal anti-inflammatory drug use in Australia 1990-1994. A report from the Drug Utilisation Sub-Committee of the Pharmaceutical Benefits Advisory Committee. *Med J Aust* 1996; 164(10): 589-592

P101. Walker JW, Lockton AI, Nguyen TV, Day RO. Analgesic effect of ibuprofen after single and multiple doses in chronic spinal pain patients. *Analgesia* 1996; 2: 93-101

P102. Tett S, Day RO, Cutler D. Hydroxychloroquine relative bioavailability: within subject reproducibility. *Brit J Clin Pharmacol* 1996; 41(4): 349-350

P103. Johnson AG, Nguyen TV, Owe-Young R, Williamson DJ, Day RO. Potential mechanisms by which nonsteroidal anti-inflammatory drugs elevate blood pressure: the role of endothelin-I. *J Human Hypertension* 1996; 10(4): 257-261

P104. Handel ML, Watts CKW, Silversten S, Day RO, Sutherland RL. D-Penicillamine causes free-radical-dependent inactivation of activator protein-1 DNA binding. *Mol Pharmacol* 1996; 50(3): 501-505

P105. Graham S, Day RO, Wong H, McLachlan AJ, Bergendal L, Miners JO, Birkett DJ. Pharmacodynamics of oxypurinol after administration of allopurinol to healthy subjects. *Brit J Clin Pharmacol* 1996; 41(4):299-304

P106. Walker JS, Chandler AK, Wilson JL, Binder W, Day RO. Effect of $\mu$-opioids morphine and buprenorphine on the development of adjuvant arthritis in rats. *Inflam Res* 1996; 45(11): 557-563

P107 Walker JS, Day RO. Experimental pain techniques. *Brit J Clin Pharmacol* 1996; 41:347-350

P108. Walker JS, Sheather-Reid RB, Carmody JJ, Vial JH, Day RO. Nonsteroidal antiinflammatory drugs in rheumatoid arthritis and osteoarthritis - support for the concept of responders and nonresponders. *Arth Rheum* 1997; 40(11): 1944-1954

P109. Shackel NA, Day RO, Kellett B, Brooks PM. Copper-salicylate gel for pain relief in osteoarthritis - a randomised controlled trial. *Med J Aust.* 1997; 167(3): 134-136

P110. Conaghan PG, Crotty M, Oh E, Day RO, Brooks PM. Anti-rheumatic drug-prescribing behaviour of Australasian rheumatologists 1984-1994. *Brit J Rheumatol* 1997; 36(4): 487-490

P111. Donnelly R, Williams KM, Day RO, Seale P. Effects of budesonide and fluticasone on 24-hour plasma cortisol: A dose-response study. *Am J Respir Crit Care Med* 1997; 156(6): 1746-175

P112. Birkett DJ, Miners JO, Valente L, Lillywhite KJ, Day RO, 1-Methylxanthine derived from caffeine as a pharmacodynamic probe of oxypurinol effect. *Brit J Clin Pharmacol* 1997; 43(2): 197-200

P113. Bramley-Moore S, Wodak A, Day RO, Lauchlan R. Patterns of analgesic prescribing for patients with chronic non-malignant pain in NSW. *J Hosp Pharmacy* 1998; 28(2): 83-88

P114. Browne GS, Nelson C, Nguyen T, Ellis BA, Day RO, Williams KM. Stereoselective and substrate-dependent inhibition of hepatic mitochondrial B-oxidation and oxidative phosphorylation by 2-arylpropionates. *Inflammation Research* 1998; 28(2): 83-88

P115. Weekes LM, Brooks C, Day RO. Indicators for Drug and Therapeutics Committees. *Br J Clin Pharmacol* 1998; 45(4):393-398

P116. Scheuerer S, Williams KM, Brugger R, McLachlan AJ, Brune K, Day RO, Geisslinger G. Effect of clofibrate on the chiral disposition of ibuprofen in rats. *J Pharmacol Exp Therap* 1998; 284(3): 1132-1138

P117. McCrudden E, Day RO, Tett S. Folinic acid and methotrexate (letter). *Aust J Hosp Pharmacy* 1998; 17:451

P118. Gazarian M, Tugwell P, Boers M, Bombardier C, Brooks P, Day RO, Strand V, Wells G. Patient based methods for assessing adverse events in clinical trials in rheumatology. Progress report for the OMERACT Drug Toxicity working party. *J Rheumatology* 1999; 26:207-209

P119. Browne GS, Nelson C, Tuan N, Ellis BE, Day RO, Williams KM. Stereoselective and substrate dependent inhibition of hepatic mitochondrial b-oxidation and oxidative phosphorylation by the non-steroidal anti-inflammatory drugs ibuprofen, flurbiprofen and ketorolac. *Biochem Pharmacol* 1999; 57(7):837-44

P120 Tett SE, Cutler DJ, Beck C, Day RO. Concentration effect relationship of hydroxychloroquine in patients with rheumatoid arthritis – A prospective, dose-ranging study. *J. Rheumatology* 2000; 27(7):1656-1660

P121 O'Sullivan AJ. Kennedy MC. Casey JH. Day RO. Corrigan B. Wodak AD. Anabolic-androgenic steroids: medical assessment of present, past and potential users.
*Medical Journal of Australia.* 173(6):323-327, 2000 September 18.

P122 Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, Day R, Ferraz MB, Hawkey CJ, Hochberg MC, Kvien TK, Schnitzer TJ, Weaver A.
Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *New Engl J Med* 2000; 343(21):1520-1528

P123 Day R. Morrison B. Luza A. Castaneda O. Strusberg A. Nahir M. Helgetveit KB. Kress B. Daniels B. Bolognese J. Krupa D. Seidenberg B. Ehrich E. A randomized trial of the efficacy and tolerability of the COX-2 inhibitor rofecoxib vs ibuprofen in patients with osteoarthritis. *Archives of Internal Medicine* 2000; 160:1781-1787

P124 Carmichael SJ, Beal J, Day RO, Tett SE. Combination therapy with methotrexate and hydroxychloroquine for rheumatoid arthritis increases exposure to methotrexate. *Journal of Rheumatology* 2002; 29(10):2077 - 2083

P125 Tan E, Day RO, Brien J. Drug and therapeutics committees – are they fulfilling their potential to improve the quality use of medicines? *International Journal of Pharmacy Practice* 2003; 11:175-181

P126. Wren BG, Day RO, McLachlan AJ, Williams KM. Pharmacokinetics of estradiol, progesterone, testosterone and dehydroepiandrosterone after transbuccal administration to postmenopausal women *Climacteric* 2003; 6(2):104-111

P127 Sasongko L, Williams KM, Day RO, McLachlan AJ. Human subcutaneous tissue distribution of fluconazole: comparison of microdialysis and suction blister techniques. *British Journal of Clinical Pharmacology* 2003; 56:551-61

P128 Day RO, Brooks P, Conaghan PG, Petersen M. A double-blind, randomised, parallel group study of the effectiveness and tolerance of intra-articular hyaluronan in osteoarthritis of the knee. *Journal of Rheumatology* 2004; 31(4):775-82, 2004.

P129 Jiang X, Williams KM, Liauw WS, Ammit AJ, Roufogalis B, Duke C, Day RO, McLachlan, AJ. Effect of St John's Wort and ginseng on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects. *British Journal of Clinical Pharmacology* 2004; 57:592-599

P130 Pett SL, Williams LA, Day RO, Lloyd AR, Carr AD, Clezy KR, Emery S, Kaplan E, McPhee DA, McLachlan AJ, Gelder FB, Lewin SR, Liauw W, Williams KM. A Phase I Study of the Pharmacokinetics and Safety of Passive Immunotherapy with Caprine Anti-HIV Antibodies, (PE)HRG214, in HIV-1-Infected Individuals. *HIV Clin Trials*. 2004; 5(2):91-8.

P131 Tan E, Day RO, Brien JE. Stakeholder opinions on the implementation of Drug and Therapeutics Committee decisions. *Journal of Pharmacy Practice and Research* 2004; 34:178-182

P132 Jiang X, Williams KM, Liauw WS, Ammit AJ, Roufogalis BD, Duke CC, Day RO, McLachlan AJ. Effect of ginkgo and ginger on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects *British Journal of Clinical Pharmacology* 2005; 59(4):425-432

P133 Kerridge I, Maguire D, Newby D, McNeill PM, Henry D, Hill S, Day R, MacDonald G, Stokes B, Henderson K. Cooperative partnerships or conflicts of interest? A national survey of interactions between the pharmaceutical industry and medical organizations. *Internal Medicine Journal* 2005; 35:206-210

P134 Henry D, Kerridge I, Hill S, McNeill PM, Doran E, Newby D, Henderson K, Maguire D, Stokes B, MacDonald G, Day R. Medical specialists and pharmaceutical industry-sponsored research: a survey of the Australian experience. *Med J Aust* 2005;182(11):557-60

P135 Hamama AK, Ray J, Day RO, Brien JE. Simultaneous Determination of Rofecoxib and Celecoxib in Human Plasma by High Performance Liquid Chromatography *Journal of Chromatographic Science* 2005;43:1-4

P136 Kaye KI, Welch SA, Graudins LV, Graudins A, Rotem T, Davis SR, Day RO
Pethidine in emergency departments: promoting evidence-based prescribing
*Med J Aust* 2005; 183 (3):129-133

P.137 Hancock MJ, Maher CG, Latimer J, Andrew J McLachlan , Cooper CW , Day RO, Spindler MF, McAuley JH. Manipulative therapy and/or NSAIDs for acute low back pain: design of a randomised controlled trial. *BMC Musculoskeletal Disorders* 2005, 6:57

P138 Ritchie J, Lu C, Williams K, Day R. Sample size is beside the point in policy development research. *Australian & New Zealand Journal of Public Health* 2005, 29, no. 6, 583 (letter)

P139 Henry D, Doran E, Hill S, McNeill PM, Day R. Ties that bind. Multiple relationships between clinical researchers and the pharmaceutical industry. *Arch.Int.Med.* 2005, 165;2493-6

P140 Lu CY, Ritchie J, Williams KM, Day RO. Recent developments in targeting access to high cost medicines in Australia *Australia and New Zealand Health Policy* 2005, 2:28
(http://www.anzhealthpolicy.com/content/2/1/28)

P141 Tan EL, Brien JE, Day RO. Perspectives on Drug and Therapeutics Committee policy implementation. *Res Soc Admin Pharm* 2005; 1(4):528-545.

P142 Lu CY, Williams KM, Day RO Access to tumour necrosis factor inhibitors for rheumatoid arthritis treatment under the Australian Pharmaceutical Benefits Scheme: are we on target? *Internal Medicine Journal* 2006; 36:19–27

P143 Strand V, Conaghan P, Lohmander S, Koutsoukos AD, Hurley FL, Bird H, Brooks P, Day RO, Puhl W, Band PA. An integrated analysis of five double-blind, randomized, controlled trials evaluating the safety and efficacy of a hyaluronan product for intraarticular injection in osteoarthritis of the knee. *Osteoarthritis & Cartilage* 2006: In Press

P144 Loboz K, Gross A, Liauw W, Williams K, Day R, McLachlan A. CYP2B6 activity as measured by bupropion hydroxylation: effect of induction by rifampicin and ethnicity. *Clinical Pharmacology & Therapeutics* 2006; 80:75-84

P145 Granot R, Day R, Cohen M, Mumion B, Garrick R. *Pain Medicine* 2006. Accepted

P146 McNeill PM, Kerridge IH, Henry DA, Stokes B, Hill SR, Newby D, Macdonald GJ, Day RO, Maguire, Henderson KM. Giving and receiving of gifts between pharmaceutical companies and medical specialists in Australia. *Internal Medicine Journal* 2006; 36:1–8

P147 Colera E, Magrabi F, Westbrook JI, Kidd MR, **Day RO**. Protocol for the Quick Clinical study: a randomised controlled trial to assess the impact of an online evidence retrieval system on decision-making in general practice [ISRCTN03597773] *BMC Medical Informatics and Decision Making* 2006, 6:33 MS: 1491764364108785

P148 Pearson S, **Day R**. Patterns of analgesic and anti-inflammatory medicine use by Australian veterans *Internal Medicine Journal*.-0527-2006. Accepted

P149 McNeill P, Kerridge I, **Day R**. Gifts, Drug Samples, and other items given to medical specialists by pharmaceutical companies. *Bioethical enquiry* 2006; 3:139-148

P150 Tan EL, **Day RO**, Brien JE. Prioritizing Drug and Therapeutic Committee (DTC) Decisions: A national survey. *Pharm World Sci.* 2007. DOI 10.1007/s11096-006-9074-y

P151 Lu CY, Williams KM, **Day RO** The funding and use of high-cost medicines in Australia: the example of anti-rheumatic biological medicines *Australia and New Zealand Health Policy* 2007, 4:2 (01 Mar 2007)

# EXHIBIT RD2

Review

# Do anti-TNF agents have equal efficacy in patients with rheumatoid arthritis?

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## Abstract

Tumor necrosis factor (TNF) antagonists have dramatically improved the outcomes of rheumatoid arthritis (RA). Three agents currently available in the USA – infliximab, etanercept, and adalimumab – have been designed to modify the biologic effects of TNF. Infliximab and adalimumab are monoclonal antibodies, and etanercept is a soluble protein. The pharmacokinetic and pharmacodynamic properties of each differs significantly from those of the others. All three agents are effective and safe, and can improve the quality of life in patients with RA. Although no direct comparisons are available, clinical trials provide evidence that can be used to evaluate the comparative efficacy of these agents. Infliximab, in combination with methotrexate, has been shown to relieve the signs and symptoms of RA, decrease total joint score progression, prevent joint erosions and joint-space narrowing, and improve physical function for up to 2 years. Etanercept has been shown to relieve the signs and symptoms of RA, decrease total joint score progression, and slow the rate of joint destruction, and might improve physical function. Etanercept is approved with and without methotrexate for patients who have demonstrated an incomplete response to therapy with methotrexate and other disease-modifying anti-rheumatic drugs (DMARDs), as well as for first-line therapy in early RA, psoriatic arthritis, and juvenile RA. Adalimumab relieves the signs and symptoms of RA with and without methotrexate and other DMARDs, decreases total joint score progression, prevents joint erosions and joint-space narrowing in combination with methotrexate, and might improve physical function. When selecting a TNF antagonist, rheumatologists should weigh evidence and experience with specific agents before a decision is made for use in therapy.

Keywords: adalimumab, efficacy, etanercept, infliximab, rheumatoid arthritis

## Introduction

Rheumatoid arthritis (RA), a systemic disease, is the most common form of inflammatory arthritis [1]. The disorder has a worldwide prevalence of about 1% and an annual incidence of 3 per 10,000 adults [2,3]; it is more common in women than in men [2]. RA is accompanied by significant morbidity and mortality. Depending on the severity of the disease at onset, the risk of disability can be as high as 33%, and mortality can be increased by as much as 52%, frequently as a result of infection or circulatory disease [4]. As might be expected, patients with RA also have a significant impairment in their quality of life (QOL) [5].

The ultimate goals of treatment are the prevention or control of joint damage, the prevention of functional loss, and the relief of pain [6]. With the earlier and more aggressive use of disease-modifying anti-rheumatic drugs (DMARDs) and with the introduction of the tumor necrosis factor (TNF) antagonists during the past 5 years, the management of RA has changed markedly. Previously, treat-

ACR = American College of Rheumatology; ARMADA = Anti-TNF Research Study Program of the Monoclonal Antibody D2E7 in Patients With RA; ATTRACT = Anti-TNF Trial in RA With Concomitant Therapy; CRP = C-reactive protein; DMARDs = disease-modifying anti-rheumatic drugs; ESR = erythrocyte sedimentation rate; HAQ = Health Assessment Questionnaire; IL = interleukin; QOL = quality of life; RA = rheumatoid arthritis; s.c. = subcutaneously; TNF = tumor necrosis factor.

ment was organized in a therapeutic pyramid, in which conservative management with nonsteroidal anti-inflammatory drugs was administered for several years, followed by the addition of DMARDs in a slow and incremental fashion once radiographic evidence of bony erosions appeared [1]. Unfortunately, this approach was associated with increased morbidity, lost productivity, decreased life expectancy, and increased healthcare costs. Today, treatment with DMARDs alone, or in combination, and with TNF biologic response modifiers is initiated early in patients with RA who are at an increased risk for progressive disease [1,7,8]. The 2001 World Health Organization Collaborating Centre consensus meeting on anti-cytokine therapy guidelines identified appropriate patients eligible for anti-cytokine therapy as patients with active RA who have failed an adequate course of DMARD therapy [8]. In these guidelines, unacceptable disease activity was defined as five swollen joints plus an elevated acute-phase response such as an erythrocyte sedimentation rate (ESR) of more than 28 mm/h or a C-reactive protein (CRP) concentration of more than 20 mg/l, whereas adequate exposure was defined as a course of methotrexate at a dose of at least 20 mg/week for 3 months or a smaller dose if toxicity is a limiting factor [8]. The international consensus guidelines have provided useful additional evidence-based recommendations [9,10].

Infliximab (Remicade®; Centocor, Inc., Malvern, PA, USA), etanercept (Enbrel®; Immunex Corp, Seattle, WA, USA), and adalimumab (Humira™; Abbott Laboratories, Abbott Park, IL, USA) are designed to modulate the inflammatory cascade of RA by binding TNF, thereby decreasing its bioavailability. Various cytokines have been detected in the synovial fluid of patients with RA, both pro-inflammatory (namely TNF, interleukin-1 [IL-1], and IL-6) and anti-inflammatory (transforming growth factor-β and IL-10) [11]. With several cytokines involved in the cytokine network of RA, it was argued that the suppression of only one mediator in a cytokine network might not be sufficient to control the pathophysiologic process underlying the disease [11].

Early studies by Brennan and colleagues demonstrated that in a synovial cell culture system the secondary synthesis of IL-1 and other cytokines could be markedly reduced by targeting TNF [11,12]. This led to more active research in this direction. In summary, the role of TNF is based on (1) its ability to degrade cartilage and bone *in vitro*, (2) its arthritogenic properties in animal models, (3) the co-localization of its receptors in RA synovium and the pannus–cartilage junction, and (4) its central role in regulating the synthesis of IL-1 in cultured RA-derived synovial cells [13,14].

Infliximab, etanercept, and adalimumab have undergone extensive clinical trials that have shown them to be efficacious and safe. Although they share common properties as TNF biologic response modifiers, these agents possess distinct pharmacokinetic and pharmacodynamic profiles. In the absence of any directly comparative trials, this article seeks to place the various considerations of their efficacy in perspective. It focuses on how these agents have fared in terms of their effects on symptoms (assessed by American College of Rheumatology [ACR] response criteria), structure (based on erosion, joint-space narrowing, and Sharp scores), and physical function/QOL (based on standardized questionnaires such as the Health Assessment Questionnaire [HAQ]).

## Etanercept

Etanercept is a fusion protein consisting of the ligand-binding portion of the human p75 TNF receptor plus the Fc fragment of human IgG1 [15]. Etanercept has a terminal half-life of 102 ± 30 hours [15]. The recommended starting dose is 25 mg subcutaneously (s.c.) twice weekly, with or without methotrexate [15].

In a multicenter, double-blind, placebo-controlled, phase II trial, 180 patients with refractory RA were randomized to one of four groups: etanercept 0.25, 2, or 16 mg/m² s.c., or placebo twice weekly for 3 months [16]. The primary efficacy measure was the percentage change in swollen joint count, tender joint count, and total count of swollen and tender joints from baseline to study end point (3 months) [16]. The data were then analyzed to determine the number of patients who attained the ACR criteria for 20% improvement (ACR20) and 50% improvement (ACR50). ACR20 is defined as a 20% improvement in tender and swollen joint counts and at least three of the following disease activity variables: patient's assessment of pain, patient's global assessment of disease activity, physician's global assessment of disease activity, patient's assessment of physical function, and ESR or CRP concentration [17]. Treatment with etanercept resulted in significant dose-related reductions in disease activity. After 3 months, improvements in ACR20 criteria were demonstrated in 75% of patients in the group with the highest dose (16 mg/m²), compared with 14% of controls ($P < 0.001$). Additionally, the mean percentage reduction in the number of tender or swollen joints was significantly greater in the etanercept 16 mg/m² group than in the controls (61% versus 25%, $P < 0.001$). There were no significant safety issues. The authors concluded that monotherapy with etanercept for 3 months is safe, well tolerated, and associated with clinical improvement in the symptoms of RA.

Moreland and colleagues evaluated the efficacy of 10 mg and 25 mg doses of etanercept by using the primary efficacy end points of improvements in disease activity as determined by ACR20 and ACR50 criteria at 3 and 6 months [18]. This randomized, placebo-controlled trial involved 234 American and Canadian patients with active

RA who had demonstrated an inadequate response to DMARD therapy. The number of patients who attained the ACR criteria for 70% improvement (ACR70) and changes in scores for swollen and tender joints were also assessed at the specified time intervals. Etanercept produced a significant dose-related improvement in disease manifestation. At 3 months, a significantly greater percentage of patients in the etanercept 25 mg group achieved ACR20 and ACR70 responses than did controls (62% versus 23%, $P<0.001$ [ACR20], and 41% versus 8%, $P<0.001$ [ACR50]) [18]. At 6 months, a significantly greater percentage of patients who received etanercept 25 mg met the ACR20 and ACR50 criteria than did controls (59% versus 11%, $P<0.001$ [ACR20] and 40% versus 5%, $P<0.001$ [ACR50]) [18]. Similarly, improvements in ACR20 and ACR50 scores were reported in a significantly greater percentage of patients who received etanercept 10 mg than controls (51% versus 11%, $P<0.001$ [ACR20] and 24% versus 5%, $P<0.001$ [ACR50]). Other 6-month results showed that mean counts of tender and swollen joints were significantly reduced in the patients who received etanercept 25 mg compared with controls (56% versus 6%, $P<0.05$; 47% versus 7%, $P<0.05$, respectively) [18]. Finally, significantly more etanercept-treated patients achieved an ACR70 response than did controls. At 6 months, 15% of patients in the etanercept 25 mg group, 9% of patients in the etanercept 10 mg group, and 1% of patients in the placebo group had achieved ACR70 response ($P<0.031$ for each etanercept group compared with the placebo group) [18]. Etanercept was well tolerated, and the investigators concluded that etanercept monotherapy could safely provide rapid, significant, and sustained benefits in patients with active RA.

The long-term efficacy and safety of etanercept monotherapy in patients with DMARD-refractory RA have also been demonstrated in open-label extension studies lasting up to 5 years [19,20]. Patients from a previous long-term safety trial, in which etanercept monotherapy was investigated in adults who had not responded satisfactorily to at least one DMARD, have been followed for up to 4.3 years (median, 2.4 years) for a total of 1336 patient-years [19]. Results are now available for 479 adult patients who received etanercept as monotherapy for more than 1 year, 420 patients who received the drug for more than 2 years, 164 patients who received the drug for more than 3 years, and 12 patients who received the drug for more than 4 years [19].

Patients were evaluated by ACR criteria for disease activity. At 3.5 years, 69%, 50%, and 25% of patients had achieved ACR20, ACR50, and ACR70 responses, respectively [19]. Moreland and colleagues reported their observations on the efficacy and safety of up to 5 years of etanercept therapy in patients with RA on the basis of the experience of participants in North American trials of etanercept who decided to enroll in open-label extension studies [20]. Data on long-term efficacy were available from 159 patients who had been evaluated for more than 4 years. The results showed that 28% of these patients had no tender joints, 24% had no swollen joints, and 21% had HAQ disability scores of 0 units [20]. Safety data, which were derived from 1442 patients who had been receiving etanercept for up to 6 years, showed an overall low rate of adverse events. The frequency of infections requiring hospitalization or intravenous antibiotics was 0.04 per patient-year in the total population (3573 patient-years), equivalent to the rate in placebo groups in controlled trials [20].

The efficacy of etanercept in combination with methotrexate has been evaluated in randomized, double-blind, placebo-controlled, and open-label extension studies [21,22]. Weinblatt and colleagues conducted a 6-month randomized, placebo-controlled, double-blind trial of etanercept 25 mg s.c. twice weekly plus methotrexate in 89 patients with persistently active RA despite at least 6 months of methotrexate therapy at a stable dosage of 10–25 mg/week [21]. The primary efficacy measure was the percentage of patients who met ACR20 criteria at 24 weeks. Patients treated with the combination experienced rapid and sustained improvement. At 6 months, the ACR20 criteria were met by 71% of patients treated with the combination of etanercept and methotrexate but by only 27% of patients treated with methotrexate plus placebo ($P<0.001$). Furthermore, the ACR50 criteria were met by 39% of the patients treated with etanercept plus methotrexate but by only 3% of the patients treated with methotrexate plus placebo ($P<0.001$).

The patients who received etanercept plus methotrexate had significantly better outcomes according to other measures of disease activity. At 24 weeks, the ACR70 response criteria were met by 15% of the group receiving etanercept plus methotrexate, versus 0% of the methotrexate plus placebo group ($P=0.03$) [21]. Also at 24 weeks, patients in the etanercept plus methotrexate group had median counts of tender joint of 7 versus 17 in the methotrexate plus placebo group; these were improvements from baseline of 75% and 39%, respectively, in which patients had a median of 28 tender joints. Further, those in the etanercept plus methotrexate group had a median count of 6 swollen joints versus 11 in the methotrexate plus placebo group; these were improvements from baseline of 78% and 33%, respectively, in which patients had a median of 18 swollen joints [21]. For the HAQ data at 24 weeks, there was a 47% improvement (from median values of 1.5 units at baseline to 0.8 unit at the end of the study) in the etanercept plus methotrexate group, and there was a 27% improvement (from median values of 1.5 units at baseline to 1.1 units at the end of the study) in the methotrexate plus placebo group [21].

Adverse events included mild injection-site reactions, which occurred significantly more often in the etanercept plus methotrexate group than in the methotrexate plus placebo group (42% versus 7%, $P < 0.001$) [21]. Overall, infection (for example upper respiratory tract infections or sinusitis) was the most common adverse event, but there were no significant intergroup differences in incidence or type of infection [21].

The benefits of etanercept plus methotrexate were further confirmed in a long-term trial that involved 79 of the 89 patients who had previously participated in the trial discussed earlier [22]. Of the 79 patients who originally enrolled, 14 withdrew and 65 patients remained on therapy for a median of 44 months (maximum 47 months) [22]. A reduction in the doses of methotrexate and steroids was allowed after patients had received at least 3 months of etanercept in addition to methotrexate. As permitted by the protocol, 62% of the 66 patients assessed at 3 years either reduced (from 17.5 mg/week at baseline to 11.0 mg/week, a 37% mean reduction; $P < 0.0001$) or discontinued their methotrexate dosage, with 29% of patients discontinuing methotrexate [22]. Among the patients receiving steroids, 3-year data showed 83% of patients had a reduction (from baseline of 6.4 mg/day to 2.4 mg/day, a 63% mean reduction; $P < 0.0001$), with 56% of patients discontinuing steroids [22]. There was sustained improvement of disease activity, based on ACR response criteria, in patients treated with etanercept even though methotrexate and steroid doses were reduced or their use was discontinued.

Data from 57 patients evaluated for efficacy showed that 77%, 47%, and 23% of patients met ACR20, ACR50, and ACR70 criteria, respectively, after 3 years of therapy [22]. These studies indicate that etanercept plus methotrexate produces clinically significant and long-term benefits in patients with persistently active RA.

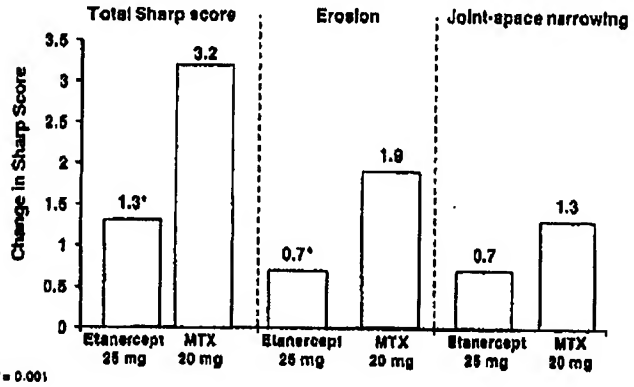
In addition to improving outcomes in patients with chronic RA, etanercept has been demonstrated to be of benefit in patients with early RA. In the Early Rheumatoid Arthritis trial, which consisted of a 1-year blinded phase ($n = 632$) [23] and a 1-year open-label extension phase ($n = 512$) [24], etanercept 10 or 25 mg s.c. twice weekly was compared with methotrexate (mean dosage 19 mg/week) in patients with active early RA (mean duration less than 3 years). ACR criteria were employed to assess treatment efficacy in terms of clinical response. The percentages of patients in the group assigned to receive etanercept 25 mg who had ACR20, ACR50, and ACR70 responses were significantly greater than those in the methotrexate group at most evaluations within the first 6 months ($P < 0.05$) but were approximately the same thereafter [23]. At 12 months, 72% of the patients in the group assigned to receive etanercept 25 mg had an ACR20 response, as compared with 65% of patients in the methotrexate group ($P = 0.16$) [23].

In the same trial, investigators compared the effects of etanercept and methotrexate on radiographic evidence of disease progression. Bone erosion and joint-space narrowing were measured radiographically and scored with the Sharp scale, in which an increase of 1 unit represents one new erosion or minimal narrowing [23–27]. The Sharp score is the sum of the erosion scores (based on a six-point scale of 0 to 5 at 46 joints) and joint-space narrowing scores (based on a five-point scale of 0 to 4 at 42 joints). In this trial the Sharp score ranged from 0 (no damage) to 398 (severe joint destruction) [23,25–27]. The 12-month data from the blinded phase showed less radiographic evidence of bone erosion in the etanercept 25 mg group than in the methotrexate group (the mean increase in erosion score was 0.47 versus 1.03 units, $P = 0.002$) [23]. There were no significant differences between the groups in progression of joint-space narrowing [23]. Patients in the etanercept 25 mg group had mean Sharp scores of $12.4 \pm 15.8$, whereas patients in the methotrexate group had mean Sharp scores of $12.9 \pm 13.8$ [23,24]. At 6 months the mean total Sharp scores increased by 0.57 unit in the etanercept 25 mg group and by 1.06 units in the methotrexate group ($P = 0.001$). At 12 months, mean total Sharp scores increased by 1.00 unit in the etanercept 25 mg group and by 1.59 units in the methotrexate group ($P = 0.11$) [23]. Data from the open-label phase showed that, at 24 months, etanercept was more effective than methotrexate in arresting structural damage on the basis of mean increases in total Sharp scores (1.3 versus 3.2 units, $P = 0.001$) and erosion scores (0.7 versus 1.9 units, $P = 0.001$) [24]. Effects of etanercept and methotrexate on joint-space narrowing at the end of 24 months were comparable (Fig. 1) [24,28].

In terms of physical function, a similar percentage of patients in the etanercept and methotrexate groups (about 55%) demonstrated an improvement in HAQ score of at least 0.5 unit at 1 year. The same proportion of etanercept-treated patients (55%) but a lower percentage of methotrexate-treated patients (37%) maintained improvement for up to 2 years ($P < 0.001$) (Fig. 2) [24]. As a point of reference, a change in HAQ score must equal at least 0.22 unit to be considered clinically significant [29].

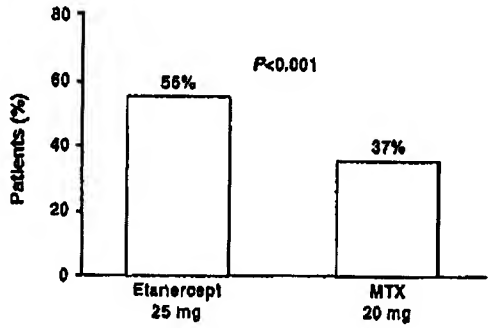
Another study showing that etanercept led to a sustained improvement in disease activity, as determined by reduction in HAQ scores, was conducted by Fleischmann and colleagues [30]. In this analysis, improvements in HAQ disability scores over 2 years were compared between 207 patients with early RA (mean duration 1 year) and 563 patients with long-standing (late) RA (mean duration 12 years), who were treated with etanercept 25 mg s.c.

**Figure 1**




Changes in total Sharp score, erosion, and joint-space narrowing at 2 years in patients who had early rheumatoid arthritis (RA) and were given etanercept or methotrexate (MTX). These were the data from the open-label extension phase of the Early Rheumatoid Arthritis trial [28].

**Figure 2**

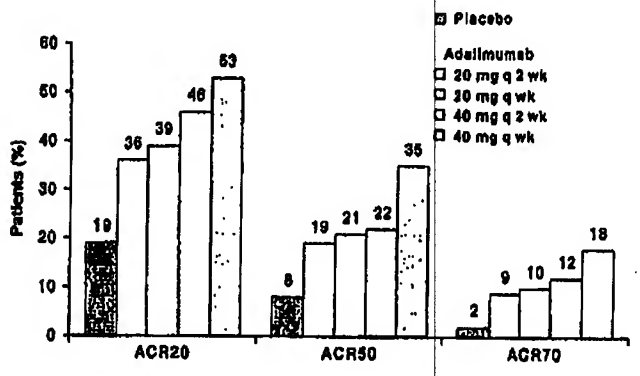



Improvement of at least 0.5 unit in health assessment questionnaire score at 2 years in patients who had early rheumatoid arthritis and were given etanercept or methotrexate (MTX). This was an open-label trial. Reproduced with permission from John Wiley & Sons, Inc. [24]. © 2002 American College of Rheumatology

twice weekly [30]. Mean baseline patient characteristics for the early RA and late RA groups were similar, including age (51 versus 53 years), HAQ (1.5 versus 1.6 units), tender joint count (31 versus 32), swollen joint count (24 versus 26), CRP concentration (3.3 versus 4.4 mg/dl), and presence of rheumatoid factor (87% versus 81%); those with early disease had been treated with fewer DMARDs (0.5 versus 3.3) [30].

Results at 2 years showed that mean HAQ scores declined in both the early RA (from 1.5 to 0.6 unit) and late RA (from 1.6 to 1.0 unit) groups. A greater percentage of patients with early disease achieved HAQ scores of 0 units, compared with those who had late disease (29% versus 14%, $P < 0.001$) [30]. The study concluded that aggressive therapy has a greater potential to improve disability, as measured by HAQ, in patients with early RA than in

**Figure 3**




Increases in ACR20, ACR50, and ACR70 scores in patients with rheumatoid arthritis who failed previous disease-modifying antirheumatic drug therapy and were given one of four dosages of adalimumab or placebo. Adapted with permission from the BMJ Publishing Group [32].

patients with more established or late RA who have not responded satisfactorily to multiple DMARDs [30].

## Adalimumab

Adalimumab, also known as D2E7, is a fully human recombinant IgG1 anti-TNF monoclonal antibody [31]. Adalimumab is available as a preparation that is administered s.c. every 2 weeks [31]. Studies indicate that adalimumab is effective and safe as biologic therapy for patients with RA, with and without methotrexate or in combination with other DMARDs.

Van de Putte and colleagues studied the efficacy and safety of adalimumab in a phase III, placebo-controlled, double-blind, 26-week trial involving 544 patients with RA who had failed treatment with one or more DMARDs [32]. After a DMARD washout period of 4 weeks, patients were randomized to one of five groups: adalimumab 20 or 40 mg s.c. weekly or biweekly, or placebo. Baseline demographics were similar for all groups. Treatment with adalimumab produced dose-related and schedule-related disease improvements measured by ACR20, ACR50, and ACR70 response criteria, with the monoclonal antibody demonstrating superiority to placebo at all dosages (Fig. 3) [32]. Adalimumab was safe and well tolerated, with the most common adverse events being injection-site reactions (9.7%), rash (9.4%), and headache (9.4%) [32].

Adalimumab plus methotrexate has been shown to be efficacious in patients who demonstrated a partial response to methotrexate alone. The Anti-TNF Research Study Program of the Monoclonal Antibody D2E7 in Patients With RA (ARMADA) study was a 24-week, randomized, double-blind, placebo-controlled, dose-ranging trial in which 271 patients with RA were administered adalimumab 20, 40, or 80 mg s.c. every 2 weeks plus

methotrexate (mean dosage 16.8 mg/week) or placebo [33,34]. Efficacy measures included the proportion of patients who attained an ACR20 response at 24 weeks (primary end point) as well as the proportion of those who met ACR50 and ACR70 response criteria at the end of the study [34].

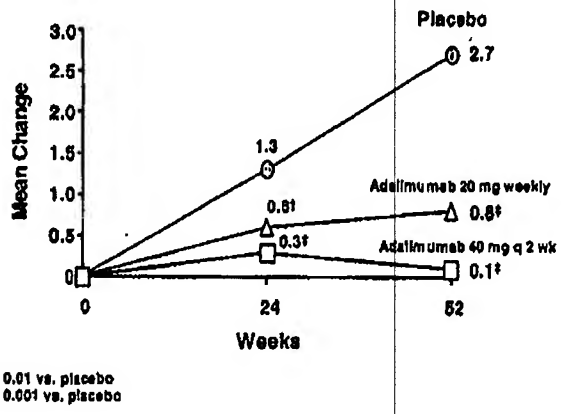
An ACR20 response at 24 weeks was attained by a significantly greater percentage of patients in the 20, 40, and 80 mg adalimumab plus methotrexate groups (47.8%, 67.2%, and 65.8%, respectively) than in the placebo plus methotrexate group (14.5%) ($P<0.001$) [34]. ACR50 response rates were attained by a significantly greater percentage of patients in the 20, 40, and 80 mg adalimumab groups (31.9%, 55.2%, and 42.5%, respectively) than in the placebo group (8.1%) ($P=0.003$, $P<0.001$, $P<0.001$, respectively) [34]. ACR 70 response rates were attained by a significantly greater percentage of patients in the 40 and 80 mg adalimumab groups (26.9% and 19.2%, respectively) than in the placebo group (4.8%) ($P<0.001$ and $P<0.02$) [34]. There were also clinically significant improvements in HAQ and physical function, where the baseline scores for the 20, 40, 80 mg, and placebo groups were 1.52, 1.55, 1.55, and 1.64 units, respectively [34]. At 24 weeks, the HAQ data showed mean reductions in scores of 0.54, 0.62, and 0.59 unit for the adalimumab 20, 40, and 80 mg groups, respectively, compared with 0.27 for the placebo group ($P=0.004$, $P<0.001$, $P<0.001$, respectively) [34].

After completing the 6-month (24-week) double-blind portion of the ARMADA trial, 250 of the original 271 patients entered an open-label extension study that evaluated the efficacy and safety of the combination of adalimumab and methotrexate over 12 months [35]. All patients received adalimumab 40 mg s.c. every other week in combination with methotrexate; 231 of the 250 patients completed 12 months of treatment [35]. Mean baseline patient characteristics were as follows: age, 55.1 years; gender, 75.6% female; positivity for rheumatoid factor, 81%; duration of RA, 12.5 years; number of previous DMARDs used, 3; and methotrexate dosage, 16.8 mg/week [35].

Results showed that when adalimumab was given to partial responders to methotrexate, clinical efficacy was sustained throughout 12 months [35]. At 12 months, the ACR20, ACR50, and ACR70 response rates for the adalimumab 40 mg group were 71.2%, 50.8%, and 26.0%, respectively [35]. With regard to QOL data at 12 months, the adalimumab 40 mg group showed a decline of 0.6 unit from baseline, which indicates that the initial response was maintained for the entire 12 months [34,35].

In a 52-week, double-blind, placebo-controlled trial involving 619 patients with active RA, treatment with adalimumab was shown to inhibit the progression of structural joint damage in patients with active RA who had an incomplete response to methotrexate therapy [36]. Patients were randomized to receive adalimumab s.c. 40 mg biweekly or 20 mg weekly, or placebo. Treatment with methotrexate (mean baseline dosage 16.6 mg/week) was initiated and continued with no change in dose over the course of the study. After 1 year there was a significant response in clinical measures of disease activity in the adalimumab-treated patients and significant differences in radiographic end points between the adalimumab-treated and placebo groups. Mean increases in the Sharp score for the adalimumab 20 and 40 mg and placebo groups were 0.8, 0.1, and 2.7, respectively ($P \leq 0.001$ versus placebo) (Fig. 4) [36]. There was a significant decrease in both joint erosions and joint-space narrowing. Thus, compared with methotrexate alone, treatment with adalimumab plus methotrexate inhibits the progression of structural joint disease in patients with RA.

**Figure 4**




Changes in total Sharp score in patients with active rheumatoid arthritis who were given one of two dosages of adalimumab or placebo. Reproduced with permission from John Wiley & Sons, Inc. [36]. © 2002 American College of Rheumatology

Adalimumab has been shown to be efficacious in patients who have failed previous DMARD therapy or have demonstrated incomplete responses to a variety of DMARDs, including methotrexate. In addition, adalimumab has been shown to inhibit radiographically evident disease progression. In each of these studies there was a significant improvement in physical function and QOL in patients for up to 1 year. Because the US Food and Drug Administration (FDA) requires at least 2 years of data showing improvement, adalimumab has not yet been approved for this indication [35,36].

## Infliximab

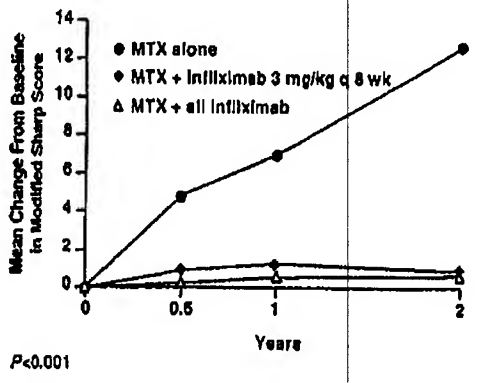
Infliximab is a chimeric IgG1-κ monoclonal antibody against TNF produced by recombinant DNA technology in

a continuously perfused cell line [37]. Unlike etanercept, infliximab does not bind lymphotoxin-α [38]: it binds both the monomeric and trimeric forms of the inflammatory cytokine TNF, forming a stable molecular complex with both molecular species. Infliximab must be administered by intravenous infusion and has a terminal half-life of 8–10 days. In managing patients with RA, the recommended dose of infliximab is 3 mg/kg initially, followed by similar doses at weeks 2 and 6, then every 8 weeks thereafter. This regimen can be adjusted by increasing the dose to 10 mg/kg and/or shortening the intervals between doses to as often as every 4 weeks to optimize patient response [37]. As of February 2002, infliximab has been administered to more than 271,000 patients (data on file, Centocor, Inc.). Infliximab in combination with methotrexate is the only regimen so far approved by the FDA for reducing symptoms, inhibiting structural damage, and improving physical function in patients with moderate-to-severe RA [37].

The efficacy and safety of infliximab in patients with RA has been demonstrated in the Anti-TNF Trial in RA With Concomitant Therapy (ATTRACT) study [39–41] and several earlier studies [42–46]. ATTRACT was a 2-year, multicenter, multinational trial of 428 patients with active RA despite methotrexate therapy. The patients were randomized to one of five regimens: infliximab 3 or 10 mg/kg intravenously every 4 or 8 weeks, or placebo [39]. All patients continued to receive a stable dose of methotrexate (median 15 mg/week for at least 6 months; range 10–35 mg/week). At 30 weeks, 50% of patients who received infliximab 3 mg/kg every 8 weeks met the ACR20 response criteria, compared with 20% of placebo recipients ($P < 0.001$) [39]. At 54 weeks, a greater percentage of patients who received infliximab 3 mg/kg every 8 weeks met ACR20, ACR50, and ACR70 response criteria than controls (42% versus 17%, $P < 0.001$ [ACR20]; 21% versus 8%, $P = 0.027$ [ACR50]; and 10% versus 2%, $P = 0.04$ [ACR70]) [40]. These improvements in the infliximab-treated patients, compared with the controls, were sustained for up to 102 weeks (42% versus 16%, $P < 0.001$ [ACR20]; 21% versus 6%, $P = 0.003$ [ACR50]; and 10% versus 1%, $P = 0.008$, respectively [ACR70]) [41]. Patients who received the infliximab 10 mg/kg regimens also showed superior improvement in ACR20, ACR50, and ACR70 response, compared with controls, for up to 102 weeks [41].

Results from the ATTRACT study indicated that infliximab halts the progression of structural joint disease and can even improve some radiographic parameters. At 54 weeks, patients treated with methotrexate plus placebo demonstrated evidence of increased joint damage, with a mean change in total Sharp score of 7 units [40]. This finding is consistent with that of other studies of structural joint damage in patients receiving DMARDs. However, patients treated with infliximab showed no evidence of progressive joint damage and had a mean change in total Sharp score of 0.6 unit by 54 weeks ($P < 0.001$) [40]. The durability of this benefit was confirmed in the 102-week ATTRACT data (Fig. 5) [39–41].

**Figure 5**




Changes in modified Sharp score in patients with active rheumatoid arthritis despite methotrexate (MTX) therapy who were given MTX alone or in combination with infliximab (the Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis With Concomitant Therapy [ATTRACT] study) [39–41].

Two-year follow-up data from the ATTRACT study showed that infliximab inhibits structural damage in RA patients with moderately-to-severely active disease as assessed by the Sharp score, bone erosion scores, and joint-space narrowing scores [39–41].

In ATTRACT, all regimens (doses/schedules) of infliximab plus methotrexate showed significantly greater improvement from baseline in HAQ and the Medical Outcomes Study Short Form Health Survey (SF-36) physical component summary score averaged over time through week 54 compared with placebo plus methotrexate [37,40]. In terms of the median (interquartile range) improvement from baseline through week 54 in HAQ, was 0.4 (0.1, 0.9) for the infliximab groups compared with 0.1 (−0.1, 0.5) for the placebo plus methotrexate group [37]. The favorable effects on HAQ and SF-36 were sustained through week 102 [37]; all infliximab-treated patients at that time showed a median improvement in HAQ of 0.3 versus 0.1 for placebo treated patients, $P < 0.001$ [41].

## Conclusion

RA causes significant functional morbidity accompanied by pain, suffering, and an impaired QOL [47]. The TNF antagonists represent a significant advance in the therapy of active RA. The three members of this class – infliximab, etanercept, and adalimumab – have shown efficacy in inhibiting joint destruction over various lengths of time, reducing symptoms, and improving physical function in

patients with RA. However, they have distinct clinical, pharmacokinetic, and pharmacodynamic properties that must be considered when selecting a drug for therapy. An integral component of the decision-making process regarding choice of therapy is patient preference. Other factors include published evidence documenting the overall experience with each drug, the duration of each trial in which the drugs were studied, the type of statistical analysis employed, and patient factors such as disease duration, disease severity at baseline, and the use of previous and concomitant medications. Careful consideration of all these clinical variables and appropriate use of the newer additions to the antirheumatic armamentarium such as the TNF biologic response modifiers will, it is hoped, contribute to better outcomes for patients with RA.

## Competing interests

SS is a speaker for Centocor, Abbott and Boehringer. RF is a consultant, on the Speaker's Bureau, and performed clinical studies for Centocor, Immunex, Amgen, Wyeth and Abbott. GJM is a consultant for Centocor, and on the Speaker's Bureau for Abbott and Centocor.

## Acknowledgement

The transcript of the World Class Debate for ACR 2002 has been published electronically in *Joint and Bone*. This article, and others published in this supplement, serve as a summary of the proceedings as well as a summary of other supportive, poignant research findings (not included in the World Class Debate ACR 2002).

## References

1. Lee DM, Weinblatt ME: **Rheumatoid arthritis.** *Lancet* 2001, 358: 903-911.
2. Spector TD: **Rheumatoid arthritis.** *Rheum Dis Clin North Am* 1990, 16:513-537.
3. Silman AJ, Pearson JE: **Epidemiology and genetics of rheumatoid arthritis.** *Arthritis Res* 2002, 4(Suppl 3):S265-S272.
4. Mikuls TR, Saag KG, Criswell LA, Merlino LA, Kaslow RA, Shelton BJ, Cerhan JR: **Mortality risk associated with rheumatoid arthritis in a prospective cohort of older women: results from the Iowa Women's Health Study.** *Ann Rheum Dis* 2002, 61: 994-999.
5. Lapsley HM, March LM, Tribe KL, Cross MJ, Courtenay BG, Brooks PM: **Living with rheumatoid arthritis: expenditures, health status, and social impact on patients.** *Ann Rheum Dis* 2002, 61:818-821.
6. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines: **Guidelines for the management of rheumatoid arthritis: 2002 update.** *Arthritis Rheum* 2002, 46: 328-346.
7. Wolfe F, Cush JJ, O'Dell JR, Kavanaugh A, Kremer JM, Lane NE, Moreland LW, Paulus HE, Pincus T, Russell AS, Wilskie KR: **Consensus recommendations for the assessment and treatment of rheumatoid arthritis.** *J Rheumatol* 2001, 28:1423-1430.
8. Emery P, Reginster JY, Appelboom T, Breedveld FC, Edelmann E, Kekow J, Malaise M, Mola EM, Montecucco C, Sanda M, Sany J, Scott DL, Serni U, Seydoux G: **WHO Collaborating Centre consensus meeting on anti-cytokine therapy in rheumatoid arthritis.** *Rheumatology (Oxford)* 2001, 40:699-702.
9. Maetzel A, Tugwell P, Boers M, Guillemin F, Coyle D, Drummond M, Wong JB, Gabriel SE: **Economic evaluation of programs or interventions in the management of rheumatoid arthritis: defining a consensus-based reference case.** *J Rheumatol* 2003, 30:891-896.
10. Emery P: **Is it time for a European consensus on the pharmacological management of early RA?** *J Rheumatol Suppl* 2002, 66:1-2.
11. Eigler A, Sinha B, Hartmann G, Endres S: **Taming TNF: strategies to restrain this proinflammatory cytokine.** *Immunol Today* 1997, 18:487-492.
12. Brennan FM, Maini RN, Feldmann M: **TNF alpha - a pivotal role in rheumatoid arthritis?** *Br J Rheumatol* 1992, 31:293-298.
13. Feldmann M: **What is the mechanism of action of anti-tumour necrosis factor-α antibody in rheumatoid arthritis?** *Int Arch Allergy Immunol* 1996, 111:362-365.
14. Maini RN, Feldmann M: **How does infliximab work in rheumatoid arthritis?** *Arthritis Res* 2002, 4(Suppl 2):S22-S28.
15. Medical Economics Company Inc: **Prescribing information: Enbrel®.** In *Physicians' Desk Reference®*. Montvale, NJ; 2002:3504-3507.
16. Moreland LW, Baumgartner SW, Schiff MH, Tindall EA, Fleischmann RM, Weaver AL, Ettlinger RE, Cohen S, Koopman WJ, Mohler K, Widmer MB, Blosch CM: **Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein.** *N Engl J Med* 1997, 337:141-147.
17. Felson DT, Anderson JJ, Boers M, Bombardier C, Chernoff M, Fried B, Furst D, Goldsmith C, Kieszak S, Lightfoot R (The Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials): **The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials.** *Arthritis Rheum* 1993, 36:729-740.
18. Moreland LW, Schiff MH, Baumgartner SW, Tindall EA, Fleischmann RM, Bulpitt KJ, Weaver AL, Keystone EC, Furst DE, Mease PJ, Ruderman EM, Horwitz DA, Arkfeld DG, Garrison L, Burge DJ, Blosch CM, Lange MLM, McDonnell ND, Weinblatt ME: **Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial.** *Ann Intern Med* 1999, 130:478-486.
19. Moreland LW, Cohen SB, Baumgartner SW, Schiff MH, Tindall EA, Burge DJ: **Long-term use of Enbrel® (etanercept) in patients with DMARD-refractory rheumatoid arthritis.** Presented at the 2nd Annual European Congress of Rheumatology (EULAR) 2001, Prague, the Czech Republic, on 15 June 2001.
20. Moreland LW, Cohen S, Fleischmann RM, Baumgartner SW, Schiff MH, Burge DJ: **Safety and efficacy of up to 5 years of etanercept (Enbrel®) therapy in rheumatoid arthritis.** Presented at the 3rd Annual European Congress of Rheumatology (EULAR) 2002, Stockholm, Sweden, on 14 June 2002.
21. Weinblatt ME, Kremer JM, Bankhurst AD, Bulpitt KJ, Fleischmann RM, Fox RI, Jackson CG, Lange M, Burge DJ: **A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate.** *N Engl J Med* 1999, 340:253-259.
22. Kremer JM, Weinblatt ME, Bankhurst AD, Bulpitt KJ, Fleischmann RM, Jackson CG, Atkins KM, Feng A, Burge DJ: **Etanercept added to background methotrexate therapy in patients with rheumatoid arthritis: continued observations.** *Arthritis Rheum* 2003, 48:1493-1499.
23. Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, Keystone EC, Genovese MC, Wasko MC, Moreland LW, Weaver AL, Markenson J, Finck BK: **A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis.** *N Engl J Med* 2000, 343:1586-1593.
24. Genovese MC, Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, Keystone EC, Wasko MC, Moreland LW, Weaver AL, Markenson J, Cannon GW, Spencer-Green G, Finck BK: **Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes.** *Arthritis Rheum* 2002, 46:1443-1450.
25. Plant MJ, Saklatvala J, Borg AA, Jones PW, Dawes PT: **Measurement and prediction of radiological progression in early rheumatoid arthritis.** *J Rheumatol* 1994, 21:1808-1813.
26. Sharp JT: **Scoring radiographic abnormalities in rheumatoid arthritis.** *Radiol Clin North Am* 1996, 34:233-241.
27. Van Der Heijde D, Simon L, Smolen J, Strand V, Sharp J, Boers M, Breedveld F, Weisman M, Weinblatt M, Rau R, Lipsky P: **How to report radiographic data in randomized clinical trials in rheumatoid arthritis: guidelines from a roundtable discussion.** *Arthritis Rheum* 2002, 47:215-218.
28. Genovese M, Martin RW, Fleischmann R, Keystone E, Bathon J, Spencer-Green G, Finck B: **Enbrel® (etanercept) vs. methotrexate (MTX) in early rheumatoid arthritis (ERA trial): two-year follow up.** Presented at the 2nd Annual European Congress of Rheumatology (EULAR) 2001, Prague, the Czech Republic, on 16 June 2001.

29. Wells GA, Tugwell P, Kraag GR, Baker PRA, Groh J, Redelmeier DA: Minimum important difference between patients with rheumatoid arthritis: the patient's perspective. *J Rheumatol* 1993, 20:557-560.
30. Fleischmann R, Baumgartner S, Moreland L, Schiff M, Markenson J, Spencer-Green G: Improvement of disability in RA patients with early vs established disease after treatment with Enbrel® (etanercept). Presented at the 2nd Annual European Congress of Rheumatology (EULAR) 2001, Prague, the Czech Republic, on 15 June 2001.
31. Abbott Laboratories: Humira: package insert. Abbott Park, IL; 2002.
32. de Putte LBA, Rau R, Breedveld FC, Kalden JR, Malaise MG, van Riel PLCM, Schattenkirchner M, Emery P, Burmester GR, Zeidler H, Montsopoulos HM, Beck K, Kupper H: Efficacy and safety of the fully human anti-tumour necrosis factor α monoclonal antibody adalimumab (D2E7) in DMARD refractory patients with rheumatoid arthritis: a 12 week, phase II study. *Ann Rheum Dis* 2003, 62:1168-1177.
33. Keystone E, Weinblatt ME, Weisman M, Furst D, Paulus H, Birbara C, Fischkoff S, Chartash EK: The fully human anti-TNF monoclonal antibody, adalimumab (D2E7), dose ranging study: the 24-week clinical results in patients with active RA on methotrexate (the ARMADA trial). Presented at the 2nd Annual European Congress of Rheumatology (EULAR) 2001, Prague, the Czech Republic, on 15 June 2001.
34. Weinblatt ME, Keystone EC, Furst DE, Moreland LW, Weisman MH, Birbara CA, Teoh LA, Fischkoff SA, Chartash EK: Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis Rheum* 2003, 48:35-45.
35. Kavanaugh AF, Weinblatt M, Keystone E, Furst DE, Moreland LW, Teoh L, Fischkoff S, Chartash E: The ARMADA trial: 12-month efficacy and safety of combination therapy with adalimumab (D2E7), the first fully human anti-TNF monoclonal antibody, and methotrexate (MTX) in patients with active rheumatoid arthritis. Presented at the 3rd Annual European Congress of Rheumatology (EULAR) 2002, Stockholm, Sweden, on 14 June 2002.
36. Keystone E, Kavanaugh AF, Sharp J, Hua Y, Teoh L, Fischkoff S, Chartash E: Adalimumab (D2E7), a fully human anti-TNF-α monoclonal antibody, inhibits the progression of structural joint damage in patients with active RA despite concomitant methotrexate therapy. *Arthritis Rheum* 2002, 46 (9 Suppl): S205.
37. Centocor, Inc.: Remicade: package insert, revised June 2002. Malvern, PA; 2002.
38. Scallon B, Cai A, Solowski N, Rosenberg A, Song XY, Shealy D, Wagner C: Binding and functional comparisons of two types of tumor necrosis factor antagonists. *J Pharmacol Exp Ther* 2002, 301:418-426.
39. Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, Smolen J, Emery P, Harriman G, Feldmann M, Lipsky P, for the ATTRACT Study Group: Infliximab (chimeric anti-tumour necrosis factor α monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: e randomised phase III trial. *Lancet* 1999, 354: 1932-1939.
40. Lipsky PE, van der Heijde DMFM, St Clair EW, Furst DE, Breedveld FC, Kalden JR, Smolen JS, Weisman M, Emery P, Feldmann M, Harriman GR, Maini RN, for the Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis With Concomitant Therapy Study Group: Infliximab and methotrexate in the treatment of rheumatoid arthritis. *N Engl J Med* 2000, 343:1594-1602.
41. Lipsky P, van der Heijde D, St Clair W, Furst D, Kalden J, Weisman M, Breedveld F, Emery P, Keystone E, Harriman G, Maini R: The ATTRACT Investigators. 102-week clinical and radiologic results from the ATTRACT trial: a 2-year, randomized, controlled, phase 3 trial of infliximab (Remicade®) in patients with active RA despite MTX. *Arthritis Rheum* 2000, 43 (Suppl 9):1216.
42. Elliott MJ, Maini RN, Feldmann M, Long-Fox A, Charles P, Katsikis P, Brennan FM, Walker J, Bijl H, Ghrayeb J, Woody JN: Treatment of rheumatoid arthritis with chimeric monoclonal antibodies to tumor necrosis factor α. *Arthritis Rheum* 1993, 36: 1681-1690.
43. Elliott MJ, Maini RN, Feldmann M, Long-Fox A, Charles P, Bijl H, Woody JN: Repeated therapy with monoclonal antibody to tumour necrosis factor alpha (cA2) in patients with rheumatoid arthritis. *Lancet* 1994, 344:1125-1127.
44. Elliott MJ, Maini RN, Feldmann M, Kalden JR, Antoni C, Smolen JS, Leeb B, Breedveld FC, Macfarlane JD, Bijl H, Woody JN: Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor α (cA2) versus placebo in rheumatoid arthritis. *Lancet* 1994, 344:1105-1110.
45. Kavanaugh A, St Clair EW, McCune WJ, Braakman T, Lipsky P: Chimeric anti-tumor necrosis factor-α monoclonal antibody treatment of patients with rheumatoid arthritis receiving methotrexate therapy. *J Rheumatol* 2000, 27:841-850.
46. Maini RN, Breedveld FC, Kalden JR, Smolen JS, Davis D, Macfarlane JD, Antoni C, Leeb B, Elliott MJ, Woody JN, Schaible TF, Feldmann M: Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor α monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum* 1998, 41:1552-1563.
47. Allaire SH, Prashker MJ, Meenan RF: The costs of rheumatoid arthritis. *Pharmacoeconomics* 1994, 6:513-522.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